Vascular Distribution of Glioblastoma Multiforme at Diagnosis

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Summary

Treatment of high-grade gliomas with selective intra-arterial (IA) administration of chemotherapies has been proposed, and utilized as a therapeutic modality. This approach offers the conceptual benefit of providing maximal delivery of the agent to the tumor bed, while potentially reducing systemic exposure to the agent. This retrospective study was designed to determine the vascular distribution of glioblastoma multiforme (GBM) at the time of diagnosis in an effort to determine what proportion of patients would likely be candidates for this approach. The preoperative MRI scans of 50 patients with GBM were analyzed and compared to published normative data of intracranial vascular distribution. Vascular distribution was determined by analyzing post-gadolinium axial and coronal T1 images, axial T2 images, and axial T2 images with an additional 1 cm margin (T2 + 1 cm) added in all dimensions. T1 analysis demonstrated 60% of tumors in a single vascular distribution. T2 analysis of these tumors reduced that number to 34%. When the T2 + 1 cm margin was utilized, only 6% of tumors were in a single vascular distribution. 66% of tumors were limited to the anterior circulation on T1 imaging but only 34% on T2 + 1 cm imaging. 30% of tumors were also within the distribution of the anterior choroidal artery. These findings suggest that the use of selective IA administration of agents is necessarily limited to a fraction of presenting patients or will require administration via multiple cerebral arteries.

Abbreviations

– *Glioblastoma Multiforme* (GBM)
– *Intra-arterial* (IA);
– *Anterior Cerebral Artery* (ACA)
– *Middle Cerebral Artery* (MCA)
– *Posterior Cerebral Artery* (PCA)

Introduction

High-grade gliomas, including glioblastoma multiforme (GBM) and anaplastic astrocytoma, are the most common primary CNS malignancies with an overall incidence of about 3.7 per 100,000 person years [1]. Median survival is approximately 15 months with 5 year survival of only 10% [2]. This poor survival rate has only shown modest improvement despite improved neuroimaging, surgical techniques, enhanced radiation technology, novel chemotherapeutic and biologic agents, and novel delivery systems.

Since the early 1980's, selective intra-arterial (IA) administration of chemotherapeutic agents has been tried, with the goal of achieving a maximal delivery to a limited volume of tissue. Initial attempts with IA chemotherapy involved hemispheric infusion via the cervical carotid artery or vertebral artery. With the advent of microcatheters, highly selective administration within one of the three major cerebral vessels of the Circle of Willis allowed delivery of therapy with a high degree of localization. Theoretically, IA administration obviates the need for higher systemic doses of therapy required to overcome the blood-brain barrier, particularly for lipid soluble agents that have high first-pass extraction. In addition, systemic side effects may be reduced.

Numerous studies have reported on the use of IA therapy. A variety of single agents have been utilized including nitrosoureas, platinum analogs, 5-FU, etoposide, or in combination with systemic chemotherapy [3]. IA administration techniques have also been used to deliver adenoviral [4] or HSV [5] vectors to human brain tumors in mice and rats with some evidence of inhibition of tumor growth. More recently, molecularly targeted therapies such as bevacizumab, a monoclonal antibody against VEGF, and cetuximab, an antibody against EGFR, has safely been delivered by IA infusion [6,7]. Each of these studies has shown some limited efficacy, although no study has shown dramatic improvements in long-term event free survival or improved response relative to systemic chemotherapy. Results rarely include information on pattern of failure; this makes it difficult to ascertain whether most tumors progressed in the region presumably treated by the IA therapy, or in other locations likely untreated by the regional administration.

The current study was undertaken to determine the location of GBM at time of diagnosis relative to the distribution of the major cerebral vessels, and to determine what proportion would be amenable to treatment with highly selective IA therapy.

Materials and Methods

We retrospectively analyzed the pre-operative brain magnetic resonance imaging (MRI) studies of all patients who had initial surgical resection of their tumor at Johns Hopkins Hospital. Successive patients were screened and included in the analysis provided their pre-operative imaging was available and pathology confirmed the diagnosis of glioblastoma multiforme. Fifty patients were included in the analysis. Using published normative data of intracranial vascular distribution [8] each tumor was evaluated for location within the frontal, temporal, parietal or occipital lobe and within the primary vascular territories of the anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA) and the anterior choroidal artery. Vascular distribution was based on the greatest axial and coronal dimensions of the tumor as determined by analysis of post-gadolinium axial and coronal T1 images and axial T2 images. We also analyzed T2 axial images with an additional 1 cm margin added in all dimensions to the tumor border to account for a presumed infiltrative edge (Figure 1). If a lesion extended to the contralateral side it was counted as two separate arterial distributions, thus allowing for tumor presence within four or more arterial distributions. A single neuroradiologist (EM) evaluated all MRI studies for confirmation of vascular distribution.

Table 1 **Arterial Distribution According to MRI Sequence**

Arterial Territory	T1 Axial	T2 Axial	T2 Axial +1 cm
ACA	13	15	24
MCA	43	47	48
PCA	17	21	33

ACA = *Anterior Cerebral Artery;* MCA = *Middle Cerebral Artery;* PCA = *Posterior Cerebral Artery*

Results

The scans of 50 patients were analyzed. Twenty-two were female and 28 male. Patients' ages ranged between 8 and 86 with a median age of 57.5 years. The tumor was centered in the frontal lobe in 15, parietal lobe in 10, temporal lobe in 21, and occipital lobe in 4. Figure

Table 2 **Location of tumor by lobe, MRI sequence and number of arterial territories**

Location	Total n (%)	T1 Axial			T2 Axial			T2 +1 cm		
		Single	Double	Triple	Single	Double	Triple	Single	Double	Triple
Frontal	15 (30%)	6 (40%)	8 (53%)	1 (17%)	5 (33%)	8 (53%)	2 (12%)	0 (0%)	7 (46%)	8 (53%)
Parietal	10 (20%)	7 (70%)	1 (10%)	2 (20%)	6 (60%)	2 (20%)	2 (20%)	1 (10%)	5 (50%)	4 (40%)
Temporal	21 (42%)	14 (67%)	7 (33%)	0 (0%)	9 (43%)	12 (57%)	0 (0%)	4 (19%)	14 (67%)	3 (14%)
Occipital	4 (8%)	3 (75%)	1 (25%)	0 (0%)	1 (25%)	2 (50%)	1 (25%)	0 (0%)	2 (50%)	2 (50%)

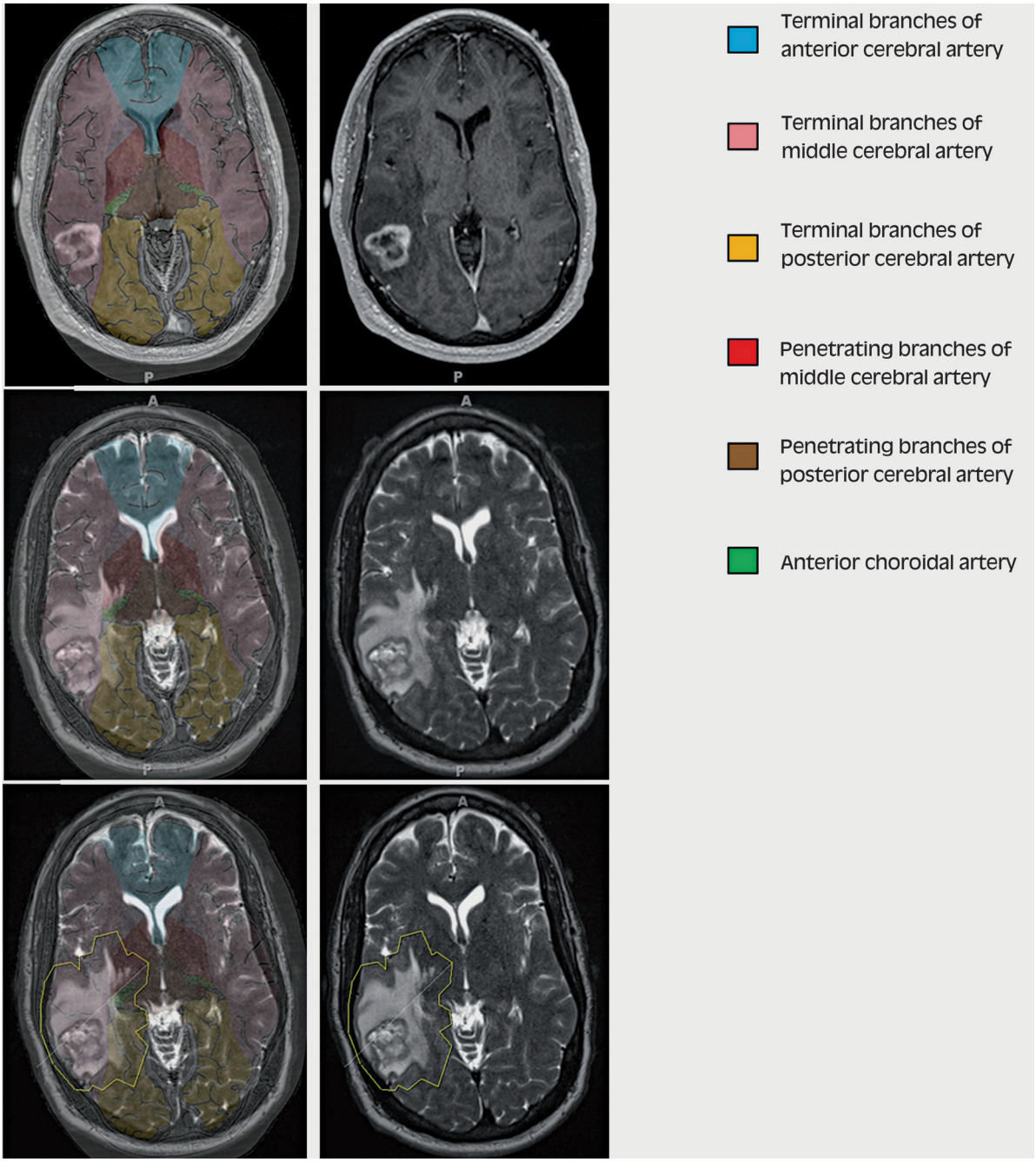

Figure 1 Representative MR images with and without overlay of vascular territories. Overlay reprinted with permission from: Kretschmann HJ and Weinrich W. Cranial Neuroimaging and Clinical Neuroanatomy. New York: Georg Thieme Verlag Stuttgart. A) Post-contrast image with overlay; B) Post-contrast without overlay; C) T2-weighted image with overlay; D) T2-weighted image without overlay; E) T2-weighted image +1 cm margin with overlay; F) T2-weighted image + 1 cm margin without overlay.

2 shows the percentage of tumors presenting in a single, double or triple arterial vessel distribution. Table 1 details which arterial territories were involved. Table 2 shows the regional distribution of tumors and the percentage of tumors in each of these territories presenting in one, two or three arterial vessel distribution. When we limited our discrimination to anterior

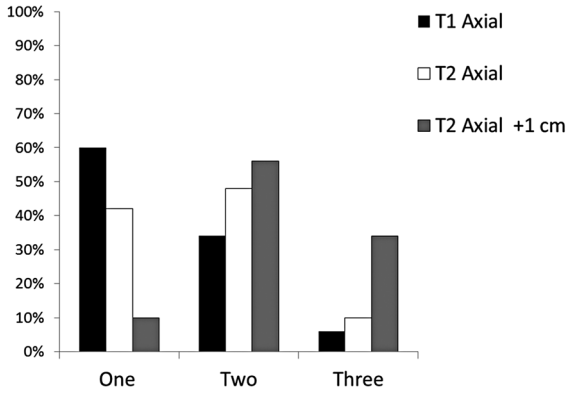

Figure 2 Percentage of tumors in one, two or three vascular territories.

(ACA + MCA) versus posterior circulation (PCA) using T1 axial images we found 66% (33/50) to be limited to the anterior circulation. However, using the T2 + 1 cm images, only 34% (17/50) were isolated to the anterior distribution, and 66% (33/50) were present in both the anterior and posterior circulation. 30% (15/50) had evidence of tumor extension within the distribution of the anterior choroidal artery (data not shown). In these instances, the tumor was present in two or more additional distributions (based on T2 + 1 cm axial images). 4% (2/50) were bilateral based on T2 imaging, but increased to 18% 19/50) when the 1 centimeter margin was added.

Discussion

The primary goal of this study was to determine the apparent vascular distribution of GBM at the time of initial presentation in an effort to determine the likely utility and feasibility of selective IA administration of therapeutic agents. While it is well known that GBM can involve multiple vascular territories, this is the first study to quantify the percentage of tumors where this is so.

Selective IA administration has been touted as a strategy to deliver high regional concentrations of therapeutics to patients with brain tumors. Our data suggests that at time of diagnosis, GBMs are unlikely to be limited to a single arterial distribution or vascular region. However, this study must be interpreted within the context of several important limitations. First, the pattern of distribution of the major cerebral arteries, though fairly constant, is subject to variability [9]. Our determination of location within vascular territories was based on normative data, and cannot reflect individual variation. To account for such variability, some have performed pre-infusion angiography to account for variations in arterial anatomy and verify vascular supply of the tumor [10]; CT-angiogram has also been utilized [11]. Second, angiogenic capabilities of some tumors could alter vascular supply to the tumor itself that are not able to be visualized with MRI. Third, tumors, such as GBM, have infiltrative leading edges, which may not be apparent using current imaging technology. By using a criterion of an additional 1 cm margin we hoped to attempt to address that limitation. Our choice of a 1 cm margin was arbitrary, but hopefully representative of the biology of GBM [12]. Less infiltrative or aggressive tumors may be more likely to fall within one vascular territory, and thus be more amenable to localized IA therapy. Fourth, though controlled for inter-rater variability by having all scans evaluated by a single, experienced neuroradiologist, we could not control for variation in imaging quality and technique given the retrospective nature of this study. Within the limited scope of the present study, at time of presentation and diagnosis, GBM is usually not limited to a single or even two arterial distributions. Localized IA administration of chemotherapeutic agents in a single arterial distribution would be unlikely to provide significant benefit to the majority of patients. To deliver chemotherapeutic agents to GBMs in a localized manner would, in the majority of patients, necessitate the catheterization of multiple cerebral arteries or the delivery of IA chemotherapy to separate territories on an alternating basis [13]. Foregoing superselective administration altogether for the supraophthalmic carotid artery may also need to be considered for tumors spanning multiple vascular territories.

Selective IA administration of chemotherapeutics carries its own set of risks. Infra-ophthalmic carotid administration has been associated with CNS and retinal toxicity [14,15], leukoencephalopathy [16] and deafness [17]. Headache, seizures, transient mental status changes, groin hematomas and urinary retention or incontinence have been reported [18]. Qureshi et al. found a low incidence of' side effects including seizure (7%), transient neurologic deficits (5%) and stroke (1%) in 100 administrations of intra-arterial carboplatin [19]. When using blood brain barrier

disruption with IA chemotherapy, complications rate were low and included deep vein thrombosis, subintimal tear, and obtundation, although 3 patients died from herniation [20].

Another novel treatment option currently being investigated is convection-enhanced delivery. This is the local administration of a therapeutic agent under positive pressure via an implanted catheter. As the catheter is implanted near the tumor site, the blood-brain-barrier is bypassed and previously unavailable chemotherapeutics and macromolecules can be utilized [21]. In addition, this technique has the potential to deliver drug to a wide region that spans multiple vascular territories, but this has been difficult to achieve in practice [22]. Understanding the vascular territories encompassed by the tumor may allow for better catheter placement and improved drug delivery. To date, there are no specific scenarios where IA delivery of chemotherapeutics is recommended over systemic therapy.

Demonstration of efficacy of IA treatment of GBM to date may have been limited by attempts to treat tumors that are present in multiple vascular territories at presentation. Improvement in outcomes in IA therapy may result if treatment is limited to those patients whose tumor is located within a single vessel distribution.

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